

FORM PTO-1390 (Modified)  
(REV 11-20/93)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

0994.00133

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

**10/019192**INTERNATIONAL APPLICATION NO.  
**PCT/US00/17341**INTERNATIONAL FILING DATE  
**23 June 2000**PRIORITY DATE CLAIMED  
**23 June 1999**

TITLE OF INVENTION

**GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS**

APPLICANT(S) FOR DO/EO/US

**Kattesh V. Katti, et al**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ has been communicated by the International Bureau.
  - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
  - a. ☐ is attached hereto.
  - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

**Items 13 to 20 below concern document(s) or information included:**

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☐ Other items or information:

U.S. APPLICATION NO. <b>10/019192</b> INTERNATIONAL APPLICATION NO. <b>PCT/US00/17341</b>				ATTORNEY'S DOCKET NUMBER <b>0994.00133</b>					
24. The following fees are submitted: <b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :</b> <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... <b>\$1040.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$890.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$740.00</b> <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$710.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100.00</b> <div style="text-align: right;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>				<b>CALCULATIONS PTO USE ONLY</b>          <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><b>\$710.00</b></td> <td style="width: 50%; border: none;"></td> </tr> <tr> <td style="border: none;"><b>\$0.00</b></td> <td style="border: none;"></td> </tr> </table>		<b>\$710.00</b>		<b>\$0.00</b>	
<b>\$710.00</b>									
<b>\$0.00</b>									
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><b>\$0.00</b></td> <td style="width: 50%; border: none;"></td> </tr> </table>		<b>\$0.00</b>			
<b>\$0.00</b>									
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE						
Total claims	7 - 20 =	0	x \$18.00	<b>\$0.00</b>					
Independent claims	4 - 3 =	1	x \$84.00	<b>\$84.00</b>					
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>					
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$794.00</b>					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				<b>\$397.00</b>					
<b>SUBTOTAL =</b>				<b>\$397.00</b>					
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				<b>\$0.00</b>					
<b>TOTAL NATIONAL FEE =</b>				<b>\$397.00</b>					
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).			<input type="checkbox"/>	<b>\$0.00</b>					
<b>TOTAL FEES ENCLOSED =</b>				<b>\$397.00</b>					
				Amount to be: refunded \$					
				charged \$					
a. <input checked="" type="checkbox"/> A check in the amount of <b>\$397.00</b> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <b>11-1449</b> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. <b>Credit card information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.									
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>									
<b>SEND ALL CORRESPONDENCE TO:</b>									
<b>Kenneth I. Kohn</b> <b>Kohn &amp; Associates</b> <b>30500 Northwestern Hwy.</b> <b>Suite 410</b> <b>Farmington Hills, Michigan 48334</b> <b>(248) 539-5050</b>				<div style="text-align: center;">             SIGNATURE         </div> <div style="text-align: center;"> <b>Kenneth I. Kohn</b>            NAME         </div> <div style="text-align: center;"> <b>30,955</b>            REGISTRATION NUMBER         </div> <div style="text-align: center;"> <b>21 December 2001</b>            DATE         </div>					

10/019172

10/019172

531 Rec'd PCT/

21 DEC 2001

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Kattesh V. Katti, et al

National Phase of PCT/US00/17341

Serial No.: Unknown

Filed: Herewith

Examiner: Unassigned

For: GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS

Our File No.: 0994.00133

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Please preliminarily amend the above application prior to  
consideration of the application on its merits, consistent with the instructions  
found attached hereto:

**AMENDED VERSION**

**GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS**

**CROSS REFERENCE TO RELATED APPLICATIONS**

The present application is a National Phase Concerning a Filing Under 35 U.S.C. 371, claiming the benefit of priority of PCT/US00/17341, filed June 23, 2000, which claims the benefit of priority of United States Provisional Serial No. 60/140,576, filed June 23, 1999 and United States Provisional Serial No. 60/156,151, filed September 27, 1999, all of which are incorporated herein by reference.

**BACKGROUND OF THE INVENTION**

**REMARKS**

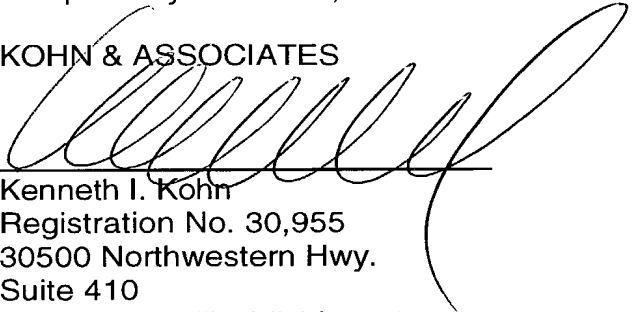
The above amendment adds no new matter and is merely made to more accurately describe and claim the invention and to claim benefit of priority.

It is respectfully submitted that the application is now in condition for allowance, which allowance is respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES

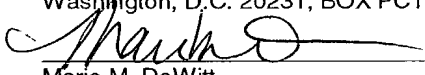
  
Kenneth I. Kohn  
Registration No. 30,955  
30500 Northwestern Hwy.  
Suite 410  
Farmington Hills, Michigan 48334  
(248) 539-5050

Dated: December 21, 2001

**CERTIFICATE OF MAILING**

Express Mail Mailing Label No.: EV 013 719 232 US

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, BOX PCT on December 21, 2001.

  
Marie M. DeWitt

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

Page 1, after the title, please insert the following paragraph:

**--CROSS REFERENCE TO RELATED APPLICATIONS**

The present application is a National Phase Concerning a Filing Under 35 U.S.C. 371, claiming the benefit of priority of PCT/US00/17341, filed June 23, 2000, which claims the benefit of priority of United States Provisional Serial No. 60/140,576, filed June 23, 1999 and United States Provisional Serial No. 60/156,151, filed September 27, 1999, all of which are incorporated herein by reference.--

**GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS****Technical Field**

5

The present invention relates to pharmaceuticals for use as therapeutic agents. More specifically, the present invention relates to pharmaceuticals containing therein gold for use as therapeutic agents.

10

**Background of the Invention**

Gold, in elemental form, has been employed for centuries as an antipruritic to relieve the itching palm. In more modern times, the observation by Robert Koch in 1890 that gold inhibited *Mycobacterium tuberculosis in vitro* led to trials in arthritis and lupus erythematosus, thought by some to be tuberculous manifestations. Later observations of success in treating chronic arthritis stimulated interest in gold therapy (chrysotherapy). At present, gold is employed in the treatment of rheumatoid arthritis; usually it is reserved for patients with progressive disease who do not obtain satisfactory relief from therapy with NSAIDs. However, gold compounds are among the agents that are used in an attempt to arrest the progress of the disease and to induce remissions; these are sometimes called disease-modifying drugs, although this is probably a misnomer (Edmonds et al., 1993). Since degenerative lesions do not regress once formed, there is an increasing tendency to attempt to induce remission early in the course of the disease. Such therapy is often initiated with gold, which although potentially beneficial, causes a high incidence of toxicity (Felson et al., 1992; Cash and Klippel, 1994).

Gold compounds can suppress or prevent, but not cure, experimental arthritis and synovitis due to a number of infectious and chemical agents.

Gold compounds have minimal antiinflammatory effects in other circumstances and cause only a gradual reduction of the signs and symptoms of inflammation associated with rheumatoid arthritis. Although many effects of these drugs have been observed, which, if any, are related to the therapeutic effects of gold in rheumatoid arthritis is unknown. Perhaps the best hypotheses relate to the capacity of gold compounds to inhibit the maturation and function of mononuclear phagocytes and of T cells, thereby suppressing immune responsiveness. Decreased concentrations of rheumatoid factor and immunoglobulins often are observed in patients who are treated with gold.

In experimental animals, gold is sequestered in organs that are rich in mononuclear phagocytes, and it selectively accumulates in the lysosomes of type A synovial cells and other macrophages within the inflamed synovium of patients who are treated with gold compounds. Moreover, the administration of gold thiomalate to animals depresses the migration and phagocytic activity of macrophages in inflammatory exudates, and chrysotherapy reduces the augmented phagocytic capacity of blood monocytes from patients with rheumatoid arthritis. Other mechanisms of action of gold compounds have been suggested, but none is generally accepted. These include inhibition of prostaglandin synthesis, interference with complement activation, cross-linking of collagen, and inhibition of the activity of lysosomal and other enzymes, including protein kinase C, in T cells.

Considerable research has been focused on the development of water-soluble gold-containing compounds because of their potential in medical applications [1]. The first application of gold-containing compounds came from their use in rheumatoid arthritis. The compounds used in the treatment of rheumatoid arthritis were aurothiomalate (Myocrisin) and aurothioglucose (Solgano) as depicted in Figure 1. In 1985, another gold containing



compound, auranofin, [(2,3,4,6-tetra-O-aceetyl-1-thio- $\beta$ -D-glucopyranosato-S)-(triethylphosphine) gold(I)] was shown to be effective for the treatment of rheumatoid arthritis [2,3]. Several studies have demonstrated that this agent is superior to the traditional chrysotherapeutic drugs. Auranofin and related gold(I) compounds have been found to be active against interperitoneal P388 leukemia and are also cytotoxic to specific tumor cells [4,5]. Mirabelli et al. screened the  $\mu$ -[bis(diphenylphosphino)ethane] digold complex [dppe(AuCl)<sub>2</sub>] (Figure 2) for antitumor activities [6]. Such digold complexes rearranged to give tetrahedral complexes of the type [Au(dppe)<sub>2</sub>].

The tetrahedral arrangement of ligands around gold (as in Au(dppe)<sub>2</sub>; Figure 2) allowed better stabilization of the metal center through chelate effects. Such tetrahedrally-bound phosphine ligands around the gold center are more inert to substitution by potential thiolate ligands that could be encountered in a biological environment.

It was suggested that the mechanism of action for [Au(dppe)<sub>2</sub>]Cl was the formation of DNA protein cross-links [7,8]. The lack of affinity of gold(I) for oxygen and nitrogen containing ligands resulted in poor reactivity with the bases of DNA.

The gold compound [Au(dppe)<sub>2</sub>]Cl demonstrated marked activity against peritoneal cancer cells. However, this compound was found to be only slightly active against solid tumor models. This compound could not proceed to clinical trials due to problems with cardiotoxicity as revealed in preclinical toxicology studies [9].

Failure to identify an effective gold-containing antitumor agent stems from the difficulties associated with the development of gold compounds with optimum hydrophilicity/lipophilicity, toxicity and activity toward specific tumors.

Therefore, an improved understanding of the molecular and biochemical mechanism of gold compounds can provide the impetus for new advances in the antitumor applications of gold compounds. It would also be useful to develop an antitumor gold compound which is not toxic to the patient.

5

It would therefore be useful to develop pharmaceuticals to develop stable non-radioactive gold complexes for use as chemotherapeutic agents.

### **Summary of the Invention**

10

According to the present invention, there is provided a complex for use as a therapeutic pharmaceutical, the complex including a ligand containing at least one hydroxyalkyl phosphine donor group bound to a gold atom to form a stable gold-ligand complex. Also provided is a method of treating cancer by administering an effective amount of a complex having a ligand of at least one hydroxyalkyl phosphine group bound to a gold atom to form a stable gold-ligand complex. Also provided is a method of preventing the metastasis of cancer and arresting cell growth by administering an effective amount of a complex having a ligand of at least one hydroxyalkyl phosphine group bound to a gold atom to form a stable gold-ligand complex.

15  
20

### **Brief Description of the Drawings**

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings wherein:

25

Figure 1 illustrates the prior art gold-containing compound;

Figure 2 illustrates further prior art gold-containing complexes;

Figure 3 illustrates representative hydroxymethyl phosphine (HMP  
5 ligands);

Figure 4 illustrates the synthesis of trihydroxymethyl phosphine gold  
complexes;

10 Figure 5 illustrates variations of alkyl chain length of hydroxymethyl  
phosphines; and

Figure 6 illustrates alternative approaches of chelating HMP groups to  
produce tetrahedral gold compounds.

15

#### **Detailed Description of the Preferred Embodiment**

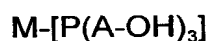
Generally, the present invention provides a complex for use as a  
therapeutic pharmaceutical. The complex includes a ligand including at least  
20 one hydroxyalkyl phosphine donor group bound to a non-radioactive gold  
atom to form a gold ligand complex that is stable. That is, the invention  
provides a ligand system containing at least one hydroxyalkyl phosphine  
donor group for use in forming complexes with non-radioactive gold metals  
wherein the complexes have high *in vitro* and/or *in vivo* stability.

25

The phosphorous ligands were chosen since the phosphorous atom  
provides a plethora of electron density that promotes formation of highly  
stable ligand metal bonds. This can occur even with non-radioactive gold  
metal in its higher oxidation states.

The hydroxyalkyl phosphine ligand is complexed with a non-radioactive gold metal, generally a gold (I) compound. These complexes contain a ratio of ligand-to-gold that is greater than or equal to 1:1 which makes the resulting  
 5 chelates small and well-defined.

A complex according to the present invention can include a complex of the formula

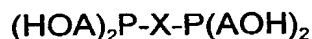


10

wherein M is non-radioactive gold metal in a reduced oxidation state, n is 1-6, and A is an alkyl group. In a preferred embodiment of the present invention, A is  $-CH_2-$ . Additionally, A can include  $-C_2H_4-$  and iso- or normal- $C_3H_6-$ .

15 The non-radioactive gold-ligand complexes can include other donor atoms or groups on the same ligand as the donor hydroxyalkyl phosphine group. These other donor groups can include N, S, O, or P atoms for coordinating the non-radioactive gold atom. In addition, the donor groups can further include amines, amides, thiols, carboxyls, and hydroxyls for  
 20 coordinating the non-radioactive gold atom.

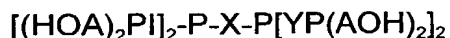
In another preferred embodiment of the present invention, the complexes can include a bidentate ligand of the formula



25 wherein A is  $-CH_2-$ ,  $-C_2H_4-$ , or iso- or normal-  $C_3H_6$ , and X is  $-(CH_2)_n-$  where  $n=1-4$ ,  $-CH_2CHR-$ ,  $-CH_2CHRCH_2-$ ,  $-CHRCH_2CH_2-$ , R'-aromatic where R' is H, an alkyl group of  $C_1-C_4$ , an aromatic group,  $-OH$ ,  $-SH$ ,  $-NH_2$ ,  $-COOH$ , activated esters, N-hydroxysuccinimides, benzyl isothiocyanate, alkyl halides, or cyclohexyldiimide. Specific examples of bidentate ligands used to complex  
 30 with gold can include 1,2-bis (bis(hydroxymethyl)phosphino)benzene (HMPB,

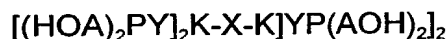
1) and 1,2-bis(bis(hydroxymethyl)phosphino)ethane (HMPE, 2) as set forth below. The formation of non-radioactive gold complexes according to the present invention with the ligands HMPB and HMPE are shown.

5 In further preferred embodiments, complexes according to the present invention are contemplated which include multidentate ligands of the formula



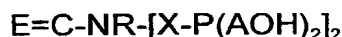
wherein A is  $-\text{CH}_2-$ ,  $-\text{C}_2\text{H}_4-$ , or iso- or normal- $\text{C}_3\text{H}_6-$ , and X is  $-(\text{CH}_2)_n-$  where  $n=1-4$ ,  $-\text{CH}_2\text{CHR}-$ ,  $-\text{CH}_2\text{CHRCH}_2-$ ,  $-\text{CHRCH}_2\text{CH}_2-$ , or  $\text{R}'$ -aromatic where  $\text{R}'$  is H, an alkyl group of  $\text{C}_1-\text{C}_4$ , an aromatic group,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{NH}_2$ ,  $-\text{COOH}$ , activated esters, N-hydroxysuccinimides, benzyl isothiocyanate, alkyl halides, or cyclohexyldiimide, and Y is  $\text{CH}_2-$ ,  $-\text{C}_2\text{H}_4-$  or  $-\text{C}_3\text{H}_6-$ . Along the lines of this embodiment, further embodiments can exist wherein all of the donor atoms can be phosphorous atoms. Additionally, embodiments are contemplated  
10 wherein at least one donor group is a hydroxyalkyl phosphine group.

Furthermore, complexes according to the present invention are contemplated wherein two donor atoms are hydroxyalkyl phosphine phosphorous-atoms and two donor atoms are atoms other than phosphorous-  
20 atoms. These complexes have the general formula



wherein A is  $-\text{CH}_2-$ ,  $-(\text{CH}_2)_2-$ , or iso- or normal- $\text{C}_3\text{H}_6-$ , K includes donor atoms or groups selected from the group consisting of  $-\text{N}-$ ,  $-\text{N}(\text{R})^+-$ ,  $-\text{N}(\text{H})-$ , Ag, and  $-\text{S}-$ , Y is  $-\text{CH}_2-$ ,  $-(\text{CH}_2)_2-$ , or iso- or normal- $\text{C}_3\text{H}_6-$ , X is  $-\text{CH}_2-$ ,  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ,  $-(\text{CH}_2)_4-$ ,  $-\text{CH}_2\text{CHR}-$ ,  $-\text{CH}_2\text{CHRCH}_2-$ ,  $-\text{CHRCH}_2\text{CH}_2-$ , or  $\text{R}'$ -aromatic wherein  $\text{R}'$  and R can be the same or different and are selected from H,  $-\text{OH}$ ,  $-\text{SH}$ ,  $-\text{NH}_2$ ,  $-\text{COOH}$ , activated esters, N-hydroxysuccinimides, benzyl isothiocyanate, alkyl halides, and cyclohexyldiimide.  
25

A variant of this embodiment can include a complex wherein two donor atoms are hydroxyalkyl phosphine phosphorous-atoms and two donor atoms are nitrogen-atoms (P2N2). These complexes can have the general formula



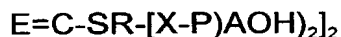
- 5 wherein X is  $-CH_2-$ ,  $-(CH_2)_2-$ ,  $-C_3H_6-$ , A is  $-CH_2-$ ,  $-(CH_2)_2-$ ,  $-C_3H_6-$ , E is O or S. R can be the same or different and is selected from H,  $-OH$ ,  $-SH$ ,  $-NH_2$ ,  $-COOH$ , activated esters, N-hydroxysuccinimides, benzyl isothiocyanate, alkyl halides, or cyclohexyl diimide.

- 10 N is nitrogen, and Y is  $-CH_2-$ ,  $-(CH_2)_2-$ , or iso- or normal- $C_3H_6-$ .

An additional embodiment is contemplated wherein two donor atoms are hydroxyalkyl phosphine phosphorous-atoms and two donor atoms are sulfur-atoms (P2S2).

15

Complexes contemplated under this embodiment have the general formula



- 20 wherein X is  $-CH_2-$ ,  $-(CH_2)_2-$ ,  $-C_3H_6-$ , A is  $-CH_2-$ ,  $-(CH_2)_2-$ ,  $-C_3H_6-$ , E is O or S. R can be the same or different and is selected from H,  $-OH$ ,  $-SH$ ,  $-NH_2$ ,  $-COOH$ , activated esters, N-hydroxysuccinimides, benzyl isothiocyanate, alkyl halides, or cyclohexyldiimide, S is sulfur, and Y is  $-CH_2-$ ,  $-(CH_2)_2-$ , or iso- or normal- $C_3H_6-$ .

- 25 A "therapeutically effective amount" is an amount of a complex of the present invention that, when administered to a patient, ameliorates a symptom of the specific disease or condition being treated. A therapeutically effective amount of a complex of the present invention can easily be determined by one skilled in the art by administering a quantity of a complex
- 30 to a patient and observing the result. In addition, those skilled in the art are

familiar with identifying patients having the particular disease or condition and are readily able to identify patients who suffer from these diseases or conditions.

- 5           The complexes of the present invention can be administered to a patient alone or as part of a composition that contains other components such as excipients, diluents, and carriers, all of which are well-known in the art. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenous, by intramuscularly or subcutaneously),  
10       intracisternally, intravaginally, intraperitoneally, intravescially, locally (powders, ointments or drops), or as a buccal or nasal spray.

- Compositions suitable for parenteral injection can comprise physiologically acceptable sterile aqueous or nonaqueous solutions,  
15       dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable  
20       organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

- These compositions can also contain adjuvants such as preserving,  
25       wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of the injectable

pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active complex is admixed with at least one customary inert excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium complexes; (g) wetting agents, as for example, acetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

20

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.

25

Solid dosage forms such as tablets, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain pacifying agents and can also be of such composition that they release the active complex or complexes in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and

30



waxes. The active complexes can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active complexes, the liquid dosage forms can contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1.3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active complexes, can contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the complexes of the present invention with suitable nonirritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a complex of this invention include ointments, powders, sprays and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservative, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The complexes and/or compositions of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 7000 mg per kilogram of body weight per day is sufficient. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the complex being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

In addition, the complexes of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

25

The complex of the present invention can be coadministered with an additional therapeutic agent. This therapeutic can include, but is not limited to, chemotherapeutic agents. Preferably, the complex of the present invention and the coadministered therapeutic agent work in conjunction with one another to create a more sustained effect. These two therapeutic agents

30

can be either administered in one pharmaceutically acceptable carrier or separately.

When the non-radioactive analogue of the gold complex of THP  
5 [(Au(THP)<sub>4</sub>)] (Figure 4) was tested for tumor cell suppression against specific human cancer cells lines, it came as a total surprise that this compound exhibited remarkable activity in suppressing tumor growth in *in vitro* conditions. The data for 50% and 70% tumor growth suppression of cells derived from human colon carcinoma are summarized in Tables 1 and 2.

10 The data in Table 1 demonstrates that 50% tumor growth suppression occurs at ~2μg of the gold compound. This invention is significant in that it demonstrates high efficacy of tumor growth suppression under extremely low doses of the new antitumor agent (Au(THP)<sub>4</sub>]Cl. The tumor growth  
15 suppression for cells derived from human gastric carcinoma have been tested. The data for 50% and 70% tumor growth suppression are summarized in Tables 2 and 4 respectively. This 50% tumor growth suppression of cells derived from human gastric carcinoma occurs at about 10mg of [Au(THP)<sub>4</sub>]Cl. This is the first demonstration that hydroxymethyl  
20 phosphine (HMP)-bound gold compounds display high efficacy in suppressing tumor growth of specific cells derived from human carcinoma.

Clinically, cisplatin is widely used as a chemotherapeutic agent in the treatment of human cancer. Use of cisplatin is generally associated with  
25 severe toxic side effects that include decrease in blood cell numbers, kidney dysfunction, etc. Therefore, cisplatin cannot be used in treating cancer patients for longer periods of time. Gold-containing compounds are less toxic and their non-toxic dose is generally higher than that of cisplatin. Therefore, it is practical to treat cancer patients using gold-containing chemotherapeutic  
30 agents for longer durations. In this context, the tumor growth suppression

data reported for [Au(THP)<sub>4</sub>]Cl demonstrates the potential of using this (and related) new generation of gold-containing compounds in treating cancer bearing patients.

5           The above discussion provides a factual basis for the use of gold-containing chemotherapeutic agents. The methods used with and the utility of the present invention can be shown by the following non-limiting examples and accompanying figures.

## 10    **EXAMPLES**

### **Example 1**

#### **Histogram Studies:**

15

Histogram studies were carried out using HCT-15 cells. In the enclosed figure that summarize histogram results the cells are numbered as follows: HCT-80 is the control; HCT-81 refers to a sample with 200 µg/ml of the gold compound; HCT-82 refers to a sample with 40 µg/ml of gold  
20    compound.

HCT-15 cells were incubated in 5% CO<sub>2</sub> incubator for two days. Then the cells were harvested and analyzed using fluorescent techniques. As shown on the enclosed figures, the percent of G1 phase in the cell cycle is  
25    significantly less for the control as compared to the cell samples that contained 200 or 40 µg of gold compound. This is an important finding because it clearly demonstrates that the gold compound elongates G1 phase and consequently slows cell growth. This finding is in sharp contrast to the cytotoxic side effects of cisplatin which is known to cause disassociation of  
30    many phases. Additionally, most agents which are cytotoxic, block S or M+

G2 phase after culturing for two days. The mode of cell suppression via G1 phase elongation, as observed for the gold compound, therefore functions differently.

5 ***In vivo* studies:**

The data of *in vivo* studies are summarized in Table: In vivo below. As shown in this table, the gold compound causes remarkable survival of tumor bearing mice. Administration of gold compound in doses significantly larger  
10 than the amount shown in this table (20-25 µg/kg) did not result in deaths of tumor bearing mice. Cisplatin at such doses resulted in the death of animals.

**Side effects:**

15 Preliminary findings, to date, have indicated no toxic cardiovascular or nephrotoxic side effects (in mice models) for the {Au[THP]<sub>4</sub>C1} compound.

**TABLE: *In vivo***  
**Results of *in vivo* study of [Au(THP)<sub>4</sub>Cl]**

5                    **Male 3.5 weeks weighing 17 to 20 g. mice.**  
**Balb/C mice inoculated 30,000 of Meth/A cells i.p. on 6/9/99**

10		mice administered with Au compound of 1 mg/kg s.c. for three times daily for three days only (3 mg/kg total) (n=17)	mice administered with Au compound of 0.2 mg/kg s.c. for three times daily for three days only (0.6 mg/kg total)(n=15)
15	<b>Control mice (n=17) date</b>		
20	6/9 0/17	0/17	0/15
	6/25 1/16	0/17	0/15
	6/26 1/15	0/17	0/15
	6/28 1/14	0/17	0/14
	6/29 1/13	0/17	0/13
25	6/30 0/13	0/17	0/13
	7/1 0/13	0/17	0/13
	7/2 3/10	1/16	1/12
	7/3 2/8	0/16	1/11
	7/5 0/8	1/15	0/11
30	7/6 0/8	0/15	1/10
	7/8 0/8	0/15	0/10
	7/9 0/8	0/15	0/10
	7/10 0/8	0/15	0/10
	7/14 0/8	0/15	0/10
35	7/20 0/2	0/15	0/10
<hr/>			
	a/b: a=number of dead mice	b=number of living mice	

40                    The data summarized in Tables 1-4 demonstrate the efficacy of  
 [Au(THP)<sub>4</sub>]Cl in suppressing tumor growth of human colon cancer and human

gastrin cancer cells. This compound is effective in treating various other carcinoma such as prostate cancer, breast cancer, brain tumors and also pancreatic cancer. The pharmacokinetic and drug action of Au-containing chemotherapeutic agents can be readily altered by systematic modifications of HMP ligands. One way is to vary the alkyl chains of alkyl hydroxy groups as shown in Figure 5. The other approach would involve utility of chelating HMP compounds such as HMPB and HMPE to produce tetrahedral gold compounds as shown in Figure 6. Therefore, chemical modifications of ligand backbones allows systematic tuning of gold pharmacophore characteristics. This aspect is important in terms of the design and development of gold-containing chemotherapeutic agents with optimum hypophilic/lipophilic characteristics and charge on the gold center that may be needed in the treatment of specific human carcinoma.

Potential applications of  $[\text{Au}(\text{THP})_4]\text{Cl}$  and related analogues include (but are not limited to): (i) treatment of small cell lung cancer; (ii) treatment of prostate cancer; (iii) treatment of breast, colon, pancreatic cancers and other kinds of malignancies; and (iv) treatment of rheumatoid arthritis.

Throughout this application, various publications, are referenced by author and year. Full citations for the publications are listed below. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

5



## REFERENCES

1. Kamei, H.; Koide, T.; Kojima, T.; Hashimoto, Y.; Hasegawa, M.  
Cancer Biotherapy & Radiopharmaceuticas. 1998, 13, 403.
- 5 2. Fricker, S.P. Transition Met. Chem. 1996, 21, 377.
3. Berglof, F.E.; Berglof, K.; Walz, D.T. J. Rheumatol. 1978, 5, 68.
4. Simon, T.M.; Kunishima, D.H.; Vibert, G.J.; Lorber, A. Cancer Res.  
1981, 41, 94.
5. Mirabelli, C.K.; Johnson, R.K.; Sung, C.M.; Faucette, L.; Muirhead, K.;  
10 Crooke, S.T. Cancer Res. 1985, 45, 32.
6. Snyder, R.M.; Mirabelli, C.K.; Johnson, R.K.; et al. Cancer Res. 1986,  
46, 5064.
7. Berners, S.J.; Jarrell, P.S.; Sadler, P.J. Inorg. Chem. 1987, 26, 3074.
8. Sadler, P. Agnew, Chem. Int. Ed. 1999, 38, 1512.
- 15 9. Hoke, G.D.; Macia, R.A.; Meunier, P.J.; Bugelski, P.J.; Mirabelli, C.K.;  
Rush, G.F.; Matthews, W.D. Toxicol. Appl. Pharmacol. 1989, 100, 293.
10. Volkert, W.A.; Goeckeler, W.F.; Ehrhardt, G.J.; Ketring, A.R. J. Nucl.  
Med. 1991, 32, 174.
11. Schubiger, P.A.; Alberto, R.; Smith, A. Bioconjugate Chem. 1996, 7,  
20 165.
12. Shi, J.C.; Huang, X.Y.; Wu, D.X.; Liu, Q.T.; Kang, B.S. Inorg. Chem.  
1996, 35, 2742.
13. Rush, G.F.; Alberts, D.W.; Meunier, D.; Leffler, K.; Smith, P.F.  
Toxicologist 1987, 7, 59.
- 25 14. Katti, K.V. Curr. Sci. 1996, 70, 219.
15. (a) Reddy, V.S.; Berning, D.E.; Katti, K.V.; Barnes, C.L.; Volkert, W.A.;  
Ketring, A.R. Inorg. Chem. 1996, 35, 1753. (b) Reddy, V.S.; Katti, K.V.;  
Barnes, C.L. J. Chem. Soc. Dalton Trans. 1996, 1301. (c) Reddy, V.S.; Katti,  
K.V.; Barnes, C.L. Inorg. Chem. Acta. 1995, 240, 367.
- 30 16. Berning, D.E.; Katti, K.V.; Sing, P.R.; Kiggenbotham, C.; Reddy, V.S.;  
Volkert, W.A. Nucl. Med. Biol. 1996, 23, 617.

WO 00/78306

PCT/US00/17341

17. Smith, C.J.; Katti, K.V. et al. Nucl. Med. Biol. 1997, 24, 685.
18. Berning, D.E.; Katti, K.V. et al. Nucl. Med. Biol. 1998, 25, 577.

**CLAIMS**

What is claimed is:

- 5           1.       A complex for use as a therapeutic pharmaceutical, said complex comprising:  
              a ligand comprising at least one hydroxyalkyl phosphine donor group bound to a non-radioactive gold atom to form a stable gold-ligand complex.
- 10           2.       The complex according to claim 1, wherein said gold atom is a gold(I) compound.
3.       The complex according to claim 1 wherein said gold-ligand complex further includes a pharmaceutically acceptable carrier.
- 15           4.       The complex according to claim 1, wherein said gold-ligand complex further includes therapeutic agent.
5.       A method of treating cancer comprising the steps of:  
20       administering an effective amount of a complex comprising a ligand comprising at least one hydroxyalkyl phosphine group bound to a non-radioactive gold atom to form a stable gold-ligand complex.
6.       A method of preventing the metastasis of cancer comprising the  
25       steps of:  
              administering an effective amount of a complex comprising a ligand comprising at least one hydroxyalkyl phosphine group bound to a non-radioactive gold atom to form a stable gold-ligand complex.

7. A method of arresting cell growth comprising the steps of:  
administering an effective amount of a complex comprising a ligand  
comprising at least one hydroxyalkyl phosphine group bound to a non-  
5 radioactive gold atom to form a stable gold-ligand complex.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number  
WO 00/78306 A1

(51) International Patent Classification<sup>7</sup>: A61K 31/28

J. [US/US]; 3220 S. Old Ridge Road, Columbia, MO 65203 (US).

(21) International Application Number: PCT/US00/17341

(22) International Filing Date: 23 June 2000 (23.06.2000)

(74) Agents: KOHN, Kenneth, I. et al.; Kohn & Associates, Suite 410, 30500 Northwestern Highway, Farmington Hills, MI 48334 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/140,576 23 June 1999 (23.06.1999) US  
60/156,151 27 September 1999 (27.09.1999) US

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): THE CURATORS OF THE UNIVERSITY OF MISSOURI [US/US]; 615 Locust Street Building, 3rd floor, Columbia, MO 65211-1400 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventor: KAMEI, Hideo (deceased).

**Published:**

— With international search report.

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): KATTI, Kattesh, V. [IN/IN]; 3901 Woods Edge Road, Columbia, MO 65203 (US). VOLKERT, Wynn, A. [US/US]; 2808 Butternut Ct., Columbia, MO 65203 (US). HOFFMAN, Timothy,

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS

(57) Abstract: There is provided a complex for use as a therapeutic pharmaceutical, the complex has a ligand containing at least one hydroxyalkyl phosphine donor group bound to a gold atom to form a stable gold-ligand complex. Also provided is a method of treating cancer by administering an effective amount of a complex having a ligand of at least one hydroxyalkyl phosphine group bound to a gold atom to form a stable gold-ligand complex. Also provided is a method of preventing the metastasis of cancer and arresting cell growth by administering an effective amount of a complex having a ligand of at least one hydroxyalkyl phosphine group bound to a gold atom to form a stable gold-ligand complex.

WO 00/78306 A1

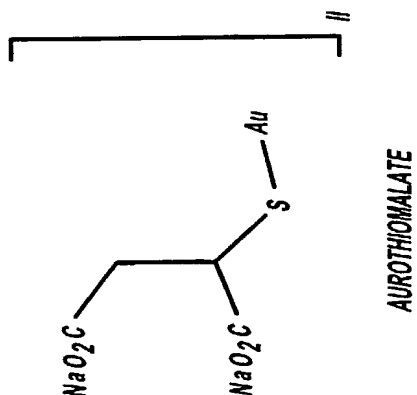
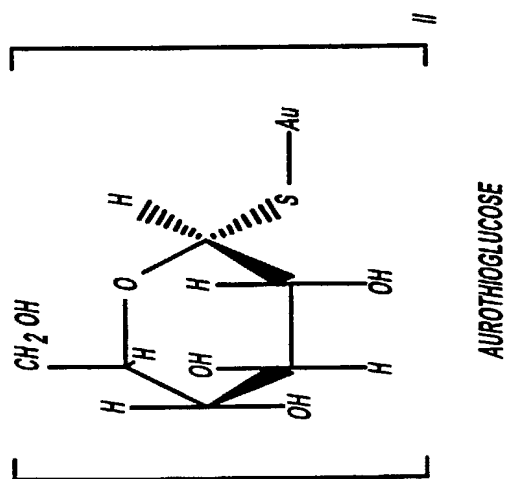
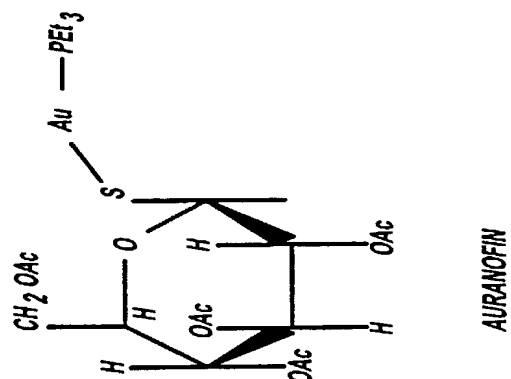


Figure - 1

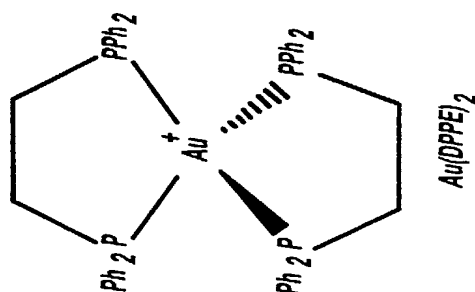
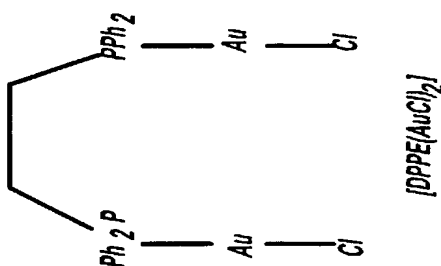


Figure - 2



REPRESENTATIVE HYDROXYMETHYL PHOSPHINE(HMP) LIGANDS

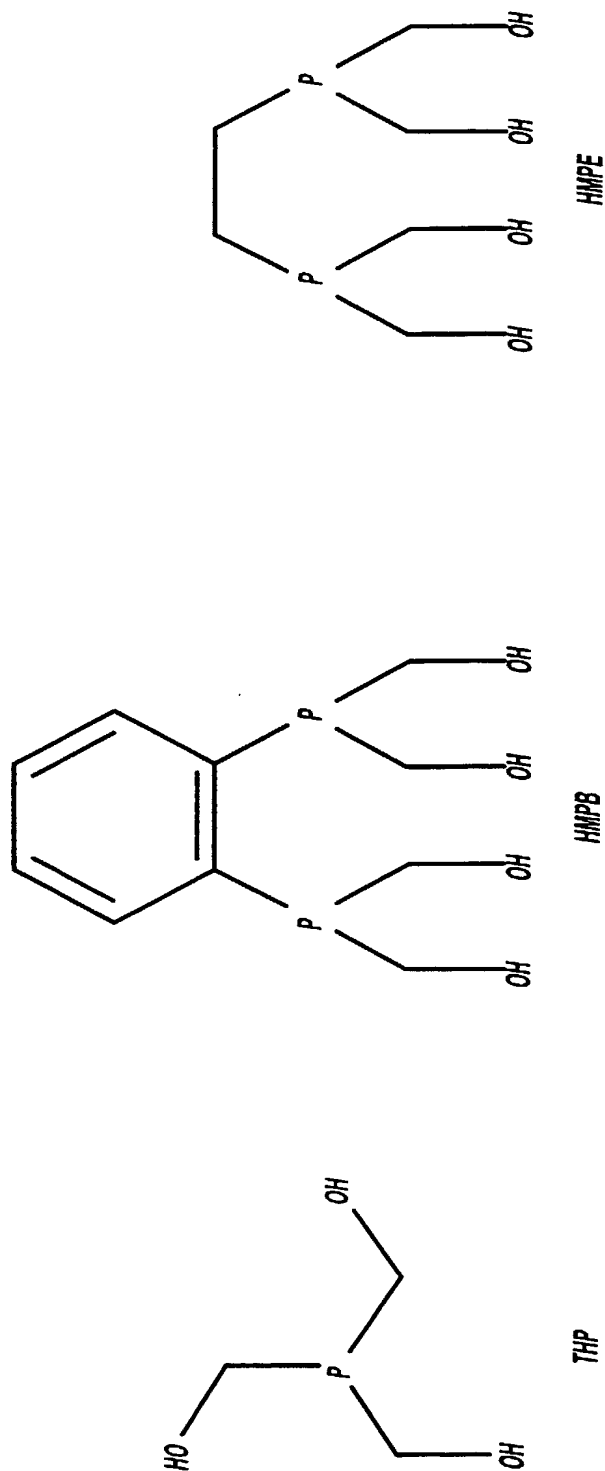
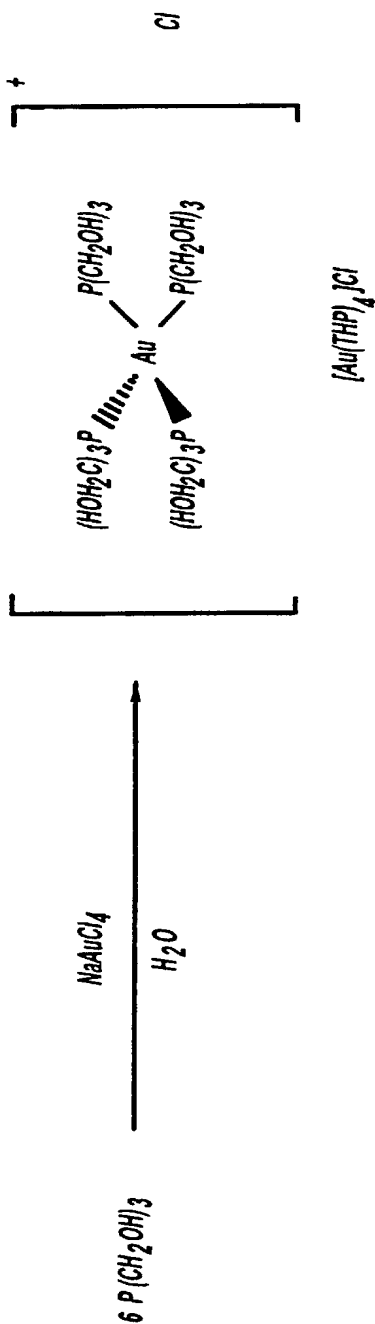


Figure - 3



## SYNTHESIS OF TRIHYDROXYMETHYL PHOSPHINE GOLD COMPLEXES

Figure - 4

VARIATIONS OF ALKYL CHAIN LENGTHS OF HYDROXYMETHYL PHOSPHINES

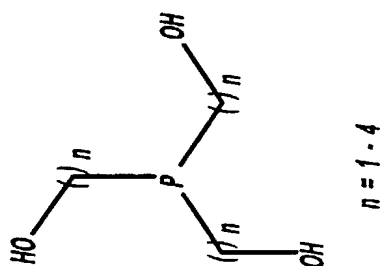


Figure - 5

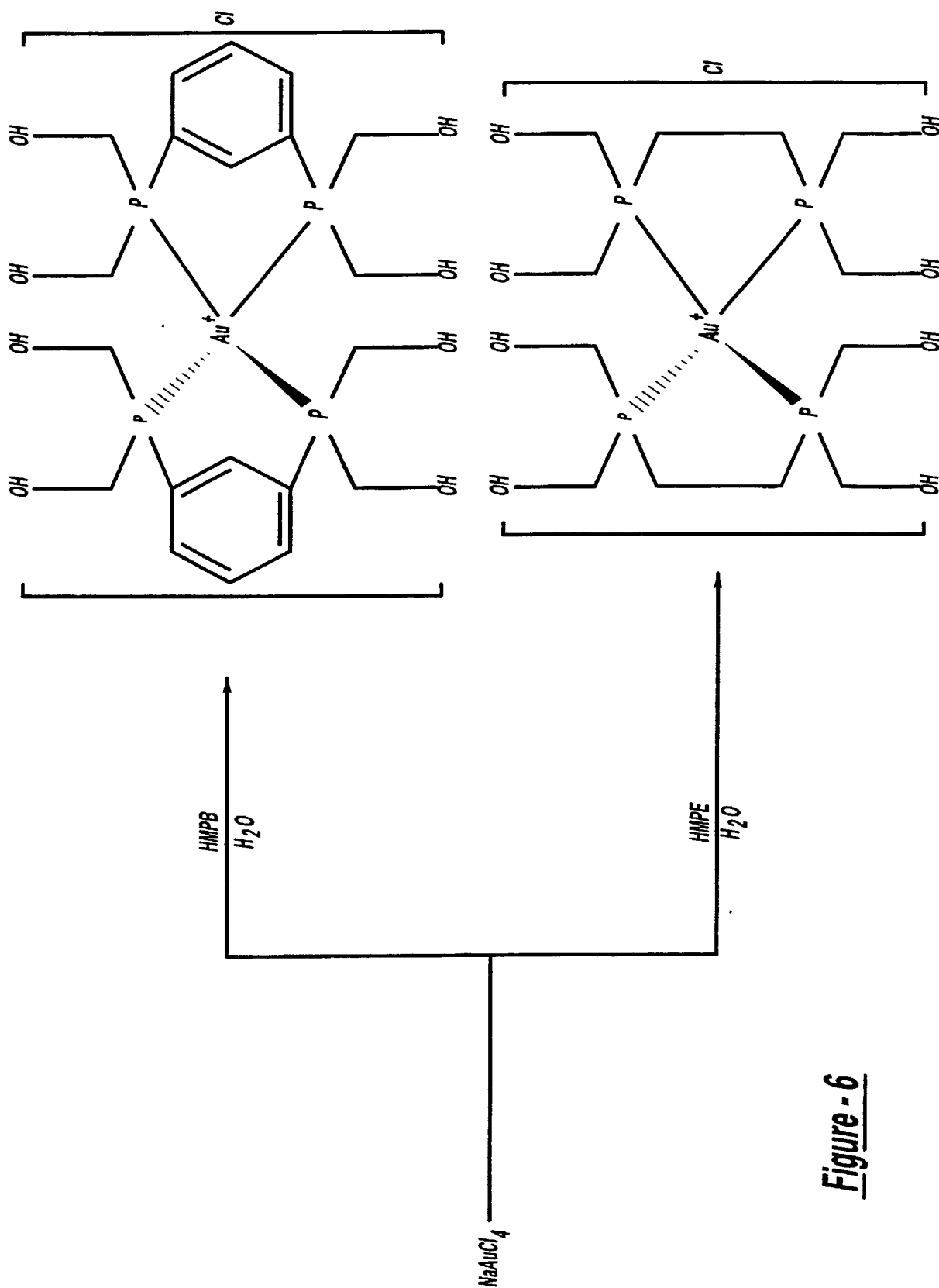


Figure - 6

Docket No.  
0994.00133

## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled  
**GOLD-CONTAINING CHEMOTHERAPEUTIC AGENTS**

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as United States Application No. or PCT International Application Number \_\_\_\_\_ and was amended on \_\_\_\_\_

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/140,576</u>	<u>23 June 1999</u>
(Application Serial No.)	(Filing Date)
<u>60/156,151</u>	<u>27 September 1999</u>
(Application Serial No.)	(Filing Date)
<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

<u>PCT/US00/17341</u>	<u>23 June 2000</u>	<u>pending</u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u>                    </u>	<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u>                    </u>	<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

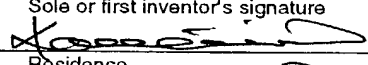
POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

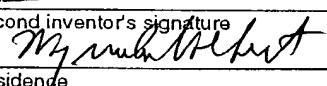
3 Kenneth I. Kohn (30,955)  
Andrew M. Parial (P50,382)

Amy E. Rinaldo (45,791)

Send Correspondence to: Kenneth I. Kohn  
Kohn & Associates  
30500 Northwestern Hwy., Suite 410  
Farmington Hills, Michigan 48334

Direct Telephone Calls to: (name and telephone number)  
(248) 539-5050

Full name of sole or first inventor <u>Kattesh V. Katti</u>	
Sole or first inventor's signature 	Date <u>01/09/02</u>
Residence <u>3901 Woods Edge Road, Columbia MO 65203</u> <u>MO</u>	
Citizenship <u>IN</u>	
Post Office Address <u>3901 Woods Edge Road, Columbia MO 65203</u>	

Full name of second inventor, if any <u>Wynn A. Volkert</u>	
Second inventor's signature 	Date <u>01/10/02</u>
Residence <u>2808 Butternut Ct., Columbia MO 65203</u> <u>MO</u>	
Citizenship <u>US</u>	
Post Office Address <u>2808 Butternut Ct., Columbia MO 65203</u> <u>MO</u>	

300

Full name of third inventor, if any <b>Timothy Hoffman</b>	
Third inventor's signature <i>Timothy Hoffman</i>	Date <i>1/12/02</i>
Residence <b>3220 S. Old Ridge Road, Columbia, MO 65203</b>	<i>MO</i>
Citizenship <b>US</b>	
Post Office Address <b>3220 S. Old Ridge Road, Columbia, MO 65203</b>	

Full name of fourth inventor, if any	
Fourth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of fifth inventor, if any	
Fifth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of sixth inventor, if any	
Sixth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of third inventor, if any <b>Timothy Hoffman</b>	
Third inventor's signature <i>Timothy Hoffman</i>	Date 1/12/02
Residence 3220 S. Old Ridge Road, Columbia, MO 65203	
Citizenship US	
Post Office Address 3220 S. Old Ridge Road, Columbia, MO 65203	

Full name of fourth inventor, if any	
Fourth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of fifth inventor, if any	
Fifth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of sixth inventor, if any	
Sixth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	